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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev. 2/95)

1- File Copy

*U.S. GPO: 2000-473-000/44602

Office Action Summary

Application No.	Applicant(s)
09/445,223	Wallach et al
Examiner	**Art Unit**
Minh-Tam Davis	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) X Responsive to communication(s) filed on *May 29, 2001*.

2a) ☐ This action is **FINAL.** 2b) X This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) X Claim(s) *5-8, 11, 12, 14-17, 19, 22-24, 29-37, and 40-50* is/are pending in the application.

4a) Of the above, claim(s) *12, 14-17, 19, 22, 29-37, 40-43, 49, and 50* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) X Claim(s) *5-8, 11, 23, 24, and 44-48* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) X Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) X Information Disclosure Statement(s) (PTO-1449) Paper No(s). *1 sheets*

18) ☐ Interview Summary (PTO-413) Paper No(s).

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Effective February 7, 1998, the Group Art Unit location has been changed, and the examiner of the application has been changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Minh-Tam Davis, Group Art Unit 1642.

Applicant's election with traverse of group I, claims 1-8, 11, 23-26, species B1 protein and fragments thereof, in Paper No. 8 is acknowledged. Applicant cancels claims 1-4, 9, 10, 13, 18, 20-21, 25-28, 38 and adds new claims 40-50. The traversal is on the ground(s) that 1) group I and group II should be examined together, because the Examiner has not alleged that the B1 protein is not novel, and thus group I and II share the same technical feature of the novel B1 protein. 2) Further, claim 49 should be examined, because Applicant is entitled to examination of a process of making a product as well as a process of using said product, and 3) Further, all other pending claims should also examined, because they share the same technical feature of novel B1 protein. This is not found persuasive because 1) B1 protein is an additional product, wherein the structure of B1 protein is patentably distinct from the structure of a DNA sequence encoding B1 protein. Thus it is appropriate to separate B1 protein as a separate group, 2) Claim 49, drawn to a method for the modulation of the effect on cells of the B1 polypeptide, comprising introducing into said cells a DNA sequence encoding said polypeptide, is a second method of use of the claimed DNA sequence. Claim 49 is patentably different from the first method of use of said DNA sequence for producing a polypeptide, as claimed in claims 11 of group I, in method's objectives, reagents and

method steps, and 3) all other pending claims are patentably distinct from the product and method of group I for the reasons set forth in previous Office action.

After review and reconsideration, the species DNA sequences encoding analogs and derivatives of B1, but not the species isoforms, are rejoined with DNA sequences encoding B1 protein and fragments thereof.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 5-8, 11, 23-24, 44-48, species DNA sequences encoding B1 protein, fragment, analogs and derivatives thereof are examined in the instant application.

Since applicant has elected Group I, a nucleic acid encoding a B1 protein, for action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, the embodiments of new claims 40-43, directed to B1 protein, and new claims 49, 50, directed to methods for the modulation of the effect on cells of the B1 polypeptide, have been withdrawn from consideration as being directed to a non-elected invention and a nucleic acid encoding B1 protein will be examined. See 37 C.F.R. § 1.142(b) and M.P.E.P. § 821.03. Newly submitted claims 40-43, 49-50 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

1) The structure of the B1 protein in claims 40-43 is different from the structure of the DNA sequence encoding the B1 protein of the elected group I.

2) The methods of claims 49-50 are patentably distinct from the method of the elected group I, in method's objectives, reagents and method steps.

SPECIFICATION

A substitute specfication is required because the specification was submitted without an adequate margin on top, and holes punched through the specification in order to insert it into patent office files have obliterated words which make it difficult to consider the application. A substitute specfication will be accepted if aplicant submits therewith a marked-up copy which shows the portions of the original specification which are being added and deleted, and a statement that the substtute specification includes no new matter and that the substitute specification includes the same changes as are indicated in the marked-up copy of the original specification showing additions and deletions. Such statement must be a verified statement if made by a person not registered to practice before the Office. Additions should be clearly indicated in the marked-up copy such as by underlining, and deletions should be indicated between brackets.

REJECTION UNDER 35 USC 112, SECOND PARAGRAPH

Claims 5-8, 11, 23, 24, 44-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claims 5-8, 11, 23, 24, 44-47 are indefinite because claims 44-47, 23, 24 are dependent on non-elected claims.

2. Claims 23, 24 are indefinite for the use of the language "other pathways'. It is not clear what "other pathways" are. In addition, the metes and bounds of the patent protection claimed cannot be determined.

3. Claim 24 is indefinite, because it is not clear what is "a mRNA sequence encoding of the B1 protein mRNA sequence".

4. Claim 11, 44-48 are indefinite for the use of the language "a polypeptide which directly or indirectly potentiates cell death". It is not clear how a polypeptide directly or indirectly potentiates cell death. This rejection could be obviated by deleting the terms "directly' and "indirectly".

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

The following is a quotation of the first paragraph of 35 USC 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 5-8, 11, 23, 24, 44, 46 and 48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Claims 5-8, 11, 23, 24, 44, 46, 48 are drawn to 1) a nucleotide sequence encoding an "analog" of a polypeptide sequence of SEQ ID NO:1, having no more than 10 changes in the amino acid sequence, each of said change being a substitution, deletion or insertion of a single amino acid, or 2) a "derivative" of SEQ ID NO:1, fragment or analog thereof, or 3) a portion of SEQ ID NO:2 encoding a polypeptide which potentiates cell death.

Although drawn specifically to the DNA art, the findings of *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412) are clearly relevant to the instant rejection. The court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a

genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

The specification discloses that conservative amino acid substitution can be made throughout the peptide encoded by the claimed nucleotide sequences without significantly reducing activity of B1 protein (p.25-27). The specification also discloses less conservative and more random changes could also be made (p.28, second paragraph) The specification indicates that techniques such as site-specific mutagenesis, or similar techniques are routine in the art. No further description of variants by substitution is provided in the specification. The claims 5-8, 11, 23, 24, 44 , 46 and 48 however read on a nucleotide sequence encoding derivatives of SEQ ID NO:1, wherein said derivatives have any type of substitution besides conservative substitution, at any amino acid, throughout the length of the peptide, as well as insertions and deletions. The specification and the claims do not place any limit on which amino acid to be subjected to conservative or non-conservative substitution, the type of substitution besides conservative substitution, nor the type of amino acids replacing the original amino acids. In addition, except for claim 46, and item (b) of claim 40 to which claims 5-8, 11, 23, 24, 44 , 48 depend on, the rest of the pending claims do not place any limit on the number of amino acids that could be substituted. Thus the scope of the claims includes nucleotide sequences encoding numerous structural

derivatives. Although the specification discloses that the types of changes are routinely done in the art, the specification and the claims do not provide any guidance as to which, or how many original amino acid(s) to be substituted as claimed in item (d) of claim 40, or to which type of substitution besides conservative substitution, or which amino acids could be deleted or inserted so that the claimed polypeptide could function as contemplated. Structural features, that could distinguish the claimed nucleotide sequences encoding said derivatives from the nucleotide sequences known in the art, are missing from the disclosure. No common structural attributes that identify the claimed nucleotide sequences encoding said derivatives are disclosed. In addition, no common functional attributes that identify the claimed nucleotide sequences encoding said derivatives or analogues are disclosed, because the function of polypeptide encoded by a nucleotide sequence could be abolished, even with substitution of only one amino acid of the peptide encoded by said nucleotide sequence (Burgess et al. Journal of Cell Biology, 1990, 11: 2129-2138), and because the specific region of SEQ ID NO:1 encoded by SEQ ID NO:2, which is necessary for potentiating cell death, is not known (see rejection under 112, first paragraph, written description, item No:2), wherein changes of no more than ten amino acids of SEQ ID NO:1 could abolish the function of potentiating cell death of SEQ ID NO:1, depending on where and which amino acids are changed. The general knowledge and level of skill in the art do not supplement the omitted description, because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the claimed nucleotide sequences encoding said derivatives, or analogues, SEQ ID

NO:2 alone is insufficient to describe nucleotide sequences encoding said derivatives or analogues. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number nucleotide sequences encoding said derivatives or analogues. Thus, applicant was not in possession of the claimed nucleotide sequences encoding said derivatives or analogues.

Thus, there is insufficient support of claims 5-8, 11, 23, 24, 44, 46 and 48 as provided by the Interim Written Description Guidelines published in the June 5, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645. Therefore, only isolated polynucleotide consisting of SEQ ID NO:2, but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph.

2. Claims 5-8, 11, 23, 24, 44, 47 and 48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 5-8, 11, 23, 24, 44, 47 and 48 are drawn to a DNA sequence or a portion of SEQ ID NO:2, encoding a fragment of SEQ ID NO:1, which fragment potentiates cell death.

The specification discloses that B1 protein enhances cell death not on its own presence, but requires the presence of cell death mediators, such as p55 TNF-R, Fas-R, MORT1, TRADD, RIP, ICE, ICH-1, but without direct interaction with these mediators (p.57, first and second paragraph, p.62, second paragraph). The specification further discloses that B1 contains a CARD

domain (p.53). Although the specification discloses that B1 contains CARD domain (p.53), which usually serves as a region through which various proteins interact during the apoptotic signaling process intracellularly, said CARD domain from the claimed B1 protein does not seem to be necessary for potentiating cell death, because mutated B1 without the CARD domain still potentiates cell death (figure 5). Thus it is not clear which fragment of B1 protein is responsible for potentiating cell death. Further, the specification discloses, but without actual binding data, that preliminary results indicate that a truncated B1 having only the intermediate region and the C-terminal CARD region binds to BCL2 (p.36, Example 2(i)). The specification speculates that B1 may serve as an inhibitor of BCL2, which is known in the art to protect cells against apoptosis (p.57, third paragraph). However, there is no data indicating that B1 actually inhibits BCL2. Thus it is questionable that the intermediate region and the C-terminal CARD region is actually responsible for potentiating cell death via inhibiting BCL2, because binding to a compound does not necessarily mean that the activity of said compound is inhibited. For example, binding of a ligand to a receptor would actually enhance the activity of a receptor.

The instant specification thus fails to provide sufficient descriptive information, such as definitive strutural or functional features of the claimed polynucleotide encoding a fragment of SEQ ID NO:1, which potentiates cell death. There is no description of the conserved regions which are critical to the structure and function of the claimed fragment.

Thus, only SEQ ID NO: 2, but not the full breadth of the claims meet the written description provisions of 35 USC 112, first paragraph.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

Claims 23, 24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 23, 24 are drawn to a pharmaceutical composition for the modulation of inflammation, cell death, cell survival, comprising a recombinant vector encoding a protein capable of binding a cell surface receptor, and encoding SEQ ID NO:1, or an antisense sequence of a nucleotide sequence encoding the B1 protein.

Inherent in a pharmaceutical composition is the use thereof.

The specification discloses the intention for treating tumors or HIV-infected cells, and inflammation by introducing into the cells a DNA molecule encoding B1 protein to increase B1 expression, and thus increasing cell death (p.22). The specification discloses that by cotransfecting cells the B1-encoding construct, with other constructs encoding cell death mediators, such as p55 TNF-R, Fas-R,, RIP, it is found that B1 protein enhances cell death not on its own presence, but requires the presence of cell death mediators (p.57, first and second paragraph, p.62, second paragraph). The specification discloses that B1 protein could also induce activation of NF-κB (p.59, figure 6), wherein the effects of NF-κB is known in the art to be highly pleiotropic, and that a majority of NF-κB activating agents are inducers of immune defense (p.2, second paragraph). The specification discloses that cell survival is associated with induction of NF-κB (p.21, last

paragraph bridging first paragraph, p.22). The specification speculates that depending on which intracellular proteins with which B1 protein interacts, the modulation of cell death or cell survival may be positive or negative (p.11, first paragraph). The specification further speculates that cell death in various inflammation, autoimmune diseases, graft-vs-host reaction could be saved by administering antagonists of B1, such as anti-sense B1 sequences (p.22, last paragraph, bridging pa.23).

One could not extrapolate the teaching in the specification to the claims, because it seems that B1 protein encoded by the claimed polynucleotide could have opposite effect, i.e. increasing cell death or cell survival. It is not clear how one could control which effect of B1 protein to be exerted *in vivo* for modulating inflammation, cell death or cell survival. For example, in treating tumors, it is not clear how one could avoid the effect of B1 protein on increasing cell survival.

Further, even if one could control which effect of B1 protein to be exerted *in vivo*, the effect on cell death by B1 protein is shown only cells transfected with B1-encoding construct, together with other constructs encoding cell death mediators, such as p55 TNF-R, Fas-R or RIP, and not in cells transfected with B1-encoding construct alone. This is not the same situation with *in vivo* treatment of tumor, because there is no correlation between death of transfected cells *in vitro* and tumor cells killing *in vivo*, and especially because one of skill in the art would not have expected that the levels of cell death mediators, such as p55 TNF-R, Fas-R, RIP in tumor cells would be the same as those in transfected cells, i.e. having overexpression of the cell death mediators. Further, the *in vitro* experimental data presented is clearly not drawn to subjects with

tumor cells. Characteristics of cultured cell lines generally differ significantly from the characteristics of a primary tumor. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary -type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interations. Thus,

based on the cell culture data presented in the specification, it could not be predicted that, in the *in vivo* environment, increased B1 protein would be in any way correlated with increased tumor cell killing.

Further, as written, it is not clear how the encoded B1 polypeptide is delivered to target cells, because the encoded polypeptide seems to be expresssed together with a protein that binds to any cell surface receptor. Anti-tumor agents and those that prevent, reduce, retard or eliminate secretion of metastatic promoters, must accomplish several tasks to be effective. They must be delivered into the circulation that supplies the tumor or metastatic promotor producing cells and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. It is clear, as disclosed above that the specification does not teach how to make/use a formulation with a targeting molecule. Also, the target cell must not have an alternate means of survival despite action at the proper site for the drug. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The formulation may be inactivated *in vivo* before producing a sufficient effect, for example, by degradation, immunological activation or due to an inherently short half life of the formulation. In addition, the formulation may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where the formulation has no effect, circulation into the target area may be insufficient to carry the formulation and a large enough local concentration may not be established.

Further, at the time of filing, and since, the design and employment of anti-sense nucleic sequences was a highly unpredictable art which required extensive experimentation in the elaboration of appropriate nucleic acid constructs that, when introduced into a host cell, would effect an inhibition of expression of any particular gene or gene product. For example, the specification fails to teach the sites within the mRNA encoding region of all of the antisense oligonucleotides encompassed within the claims which would be expected to function as an effective antisense binding site. It was well known in the art at the time the invention was made that identification of such binding sites in a given mRNA species resulting in inhibition of gene expression is an unpredictable art. For instance, US Patent No. 5,585,479 discloses an effective oligonucleotide and show that moving the target just one or two bases, can greatly reduce of even eliminate, antisense activity (data disclosed in columns 15-17). US Patent No. 5,585,479 states that "there are no rational explanations or rules that would predict active sequences" Thus, in view of the unpredictability of whether all antisense molecules would function effectively to inhibit gene expression of the target B1 polynucleotide, and in the absence of evidence to the contrary, a skilled artisan would be unable to practice the claimed invention using any transgene comprising the claimed antisense sequences without undue experimentation and with a reasonable expectation of success. Further, as drawn to transgenic mice, in the field of antisense technology, according to Gura (Science, 1995, 270:575-577), researchers have many concerns. Gura discloses that "the biggest concern is that antisense compounds simply don't work the way researchers once thought they did." Other drawbacks in animal studies include difficulty getting antisense oligonucleotides

to target tissues and the existence of potentially toxic side effects such as increased blood clotting and cardiovascular problems (page 575, col 1, para 2). Another problem stems from the fact that oligonucleotides used as controls produced the same biological effects in cell culture as did the antisense compounds (page 576, col 1, para 2 and 3). In addition, Gura reports problems with synthetic antisense oligonucleotides in that unwanted and sometimes lethal side effects occurred in animal experiments, and that they block cell migration and adhesion to underlying tissue in vitro (page 576, col 3, para 1 and 3). Thus a high degree of unpredictability is associated with the use of antisense constructs employed in methods of inhibiting expression of a particular protein in an animal model. In addition, the specification fails to set forth any methodology for producing transgenic mice using transgenes comprising B1 antisense sequences. For example, an enormous combination of vectors and promoters exist in the art and Applicants have not set forth any of the combinations or parameters to determine the appropriate combinations, in combination with which B1 antisense sequences, to determine the appropriate combinations, which will be effective in blocking B1 expression in a developing transgenic mouse.

Moreover, as written the claims 23, 24 encompass a polynucleotide sequence encoding SEQ ID NO:1, or an antisense thereof, which could either increase or decrease inflammation, and increase or decrease cell death or cell survival.

The specification however only discloses that SEQ ID NO:1 could potentiate cell death the presence of cell death mediators *in vitro* in transfected cells (p.57, first and second paragraph, p.62, second paragraph). It is not clear under which conditions exposure a cell to a polynucleotide

sequence encoding SEQ ID NO:1 would result in the opposite effect, i.e. decrease cell death, or increase cell survival *in vitro*. Further, even if the antisense of SEQ ID NO:1 could be made, it is not clear how an antisense of a polynucleotide encoding SEQ ID NO:1, which reduces the expression of SEQ ID NO:1 would have the same effect as a polynucleotide encoding SEQ ID NO:1, i.e. potentiating cell death. Moreover, the specification is not enable for an antisense of SEQ ID NO:1 which could increase cell survival even *in vitro*, because although overexpression of SEQ ID NO:1 could induce cell death, it is not necessary that reduction in expression of SEQ ID NO:1 would rescue a cell from cell death, or induce cell growth, unless tested, and because potentiating cell death by SEQ ID NO:1 could be due to artificial overexpression of SEQ ID NO:1, and under normal expression condition, it is not clear how necessary is the presence of SEQ ID NO:1 for the occurence of cell death.

In addition, it is not clear what the benefit of increasing inflammation is. Further, it is not clear how exposure a cell to a polynucleotide sequence encoding SEQ ID NO:1, or an antisense thereof would decrease or increase inflammation, because although SEQ ID NO:1 could induce activation of NF-κB (p.59, figure 6), the effects of NF-κB is highly pleiotropic, as disclosed in the specification. Further, although a majority of NF-κB activating agents are inducers of immune defense, there is no correlation between inducing an immune defense and increasing or decreasing inflammation.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to use the instant

polynucleotide sequence encoding SEQ ID NO:1, or an antisense thereof for modulating inflammation, cell death or cell survival. For the above reasons, it would require undue experimentation for one of skill in the art to practice the invention.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

1. If Applicant could overcome the above 112, first paragraph, claims 5-8, 11, 23, 24, 44 and 46 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a DNA sequence of SEQ ID NO:2 , does not reasonably provide enablement for a nucleotide sequence encoding a derivative of a polypeptide of SEQ ID NO:1 . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

Claims 5-8, 11, 23, 24, 44 and 46 are drawn to a nucleotide sequence encoding an "analog" of a polypeptide sequence of SEQ ID NO:1, having no more than 10 changes in the amino acid sequence, each of said change being a substitution, deletion or insertion of a single amino acid, or a "derivative" of SEQ ID NO:1, fragment or analog thereof.

The scope of the claims includes nucleotide sequences encoding numerous structural derivatives. Applicants have not shown how to make and use the claimed DNA sequences encoding the polypeptide derivatives which are capable of functioning as that which is being disclosed.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. Such unpredictability would equally apply to DNA sequences which encode proteins. For example, replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein (Burgess et al. Journal of Cell Biology, 1990, 11: 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cell Biology, 1988, 8: 1247-1252). Similarly, it has been shown that aglycosylation of antibodies reduces the resistance of the antibodies to proteolytic degradation, while CH2 deletions increase the binding affinity of the antibodies (see Tao. et al. The Journal of Immunology, 1989, 143(8): 2595-2601, and Gillies et al. Human Antibodies and Hybridomas, 1990, 1(1): 47-54). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein.

In view of the above unpredictability, one of skill in the art would be forced into undue experimentation in order to perform the claimed invention as broadly as claimed.

2. If Applicant could overcome the above 112, first paragraph, claims 5-8, 11, 44-47 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a DNA sequence of SEQ ID NO:2, does not reasonably provide enablement for a DNA sequence of SEQ ID NO:2 encoding a polypeptide of SEQ ID NO:1. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

Claims 5-8, 11, 44-47 are drawn to a nucleotide sequence encoding a polypeptide comprising SEQ ID NO:1, an analog, a fragment or a derivative thereof.

Claims 5-8, 11, 44-47 read on a nucleotide sequence which is expressed in tissues as a polypeptide comprising SEQ ID NO:1.

The specification discloses that SEQ ID NO:1 is a deduced amino acid sequence from a full-length cDNA clone of SEQ ID NO:2 (p.53, first paragraph).

One cannot extrapolate the teaching of the specification to the enablement of the claims because there is no teaching of whether any protein product is actually produced. Those of skill in the art recognize that expression of mRNA, specific for a tissue type, does not dictate nor predict the translation of such mRNA into a polypeptide. For example, Alberts et al. (Molecular Biology of the Cell, 3rd edition, 1994, page 465) teach that translation of ferritin mRNA into ferritin polypeptide is blocked during periods of iron starvation. Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferrin receptor polypeptide is translated. Many other proteins are regulated at the translational level rather than the transcriptional level. For instance, Shantz and Pegg (Int J of Biochem and Cell Biol., 1999, Vol. 31, pp. 107-122) teach that ornithine decarboxylase is highly regulated in the cell at the level of translation and that translation of ornithine decarboxylase mRNA is dependent on the secondary structure of the mRNA and the availability of eIF-4E, which mediates translation initiation. McClean and Hill

(Eur J of Cancer, 1993, vol. 29A, pp. 2243-2248) teach that p-glycoprotein can be overexpressed in CHO cells following exposure to radiation, without any concomitant overexpression of the p-glycoprotein mRNA. In addition, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Thus, predictability of protein translation is not solely contingent on mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. For the above reasons, one of skill in the art would not be able to predict if SEQ ID NO:2 could in fact be translated into a polypeptide expression product. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

3. If Applicant could overcome the above 112, first paragraph, claims 5-8, 11, 23, 24, 44, 48 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a DNA sequence of SEQ ID NO:2, and a method for producing SEQ ID NO:1, comprising expressing a vector comprising a DNA sequence encoding SEQ ID NO:1, does not reasonably provide enablement for a DNA sequence encoding a polypeptide which "directly or indirectly" potentiates cell death, and a method for producing "any" polypeptide which "directly or indirectly" potentiates cell death, comprising expressing a vector comprising a DNA sequence encoding SEQ ID NO:1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

Claims 5-8, 23, 24, 44, 48 are drawn to a DNA sequence encoding a polypeptide which "directly or indirectly" potentiates cell death. Claim 11 is drawn to a method for producing a polypeptide which directly or indirectly potentiates cell death, comprising expressing a vector comprising a DNA sequence encoding SEQ ID NO:1. Claim 11 reads on a method for producing any polypeptide which directly or indirectly potentiates cell death, comprising expressing a vector comprising a DNA sequence encoding SEQ ID NO:1.

It is not clear how expressing a DNA sequence encoding SEQ ID NO:1 would produce any polypeptide which directly or indirectly potentiates cell death, the structure of which are not the same as the claimed SEQ ID NO:1, e.g. proteins involved in apoptosis, such as caspases or different CARD polypeptides (Bertin, US PN=6,033,855).

Further, it is not clear from the disclosure in the specification how B1 protein or SEQ ID NO:1 potentiates cell death. Therefore, it is not clear by which way B1 potentiates cell death, i.e. directly or indirectly. The specification discloses that B1 protein enhances cell death not on its own presence, but requires the presence of cell death mediators, such as p55 TNF-R, Fas-R, MORT1, TRADD, RIP, ICE, ICH-1, but without direct interaction with these mediators (p.57, first and second paragraph, p.62, second paragraph). Thus it is not clear how B1 protein potentiates cell death in the presence of cell death mediators. The specification further discloses that B1 contains a CARD domain (p.53). Although CARD domain which usually serves as a region through which various proteins interact during the apoptotic signaling process intracellularly, said CARD domain from the claimed B1 protein does not seem to be necessary for

potentiating cell death, because mutated B1 without the CARD domain still potentiates cell death (figure 5). Thus it is seems that B1 protein does not potentiate celll death via CARD domain. Further, the specification discloses, but without actual binding data, that preliminary results indicate that a truncated B1 having only the intermediate region and the C terminal CARD region binds to BCL2 (p.36, Example 2(i)). The specification speculates that B1 may serve as an inhibitor of BCL2, which is known in the art to protect cells against apoptosis (p.57, third paragraph). However, there is no data indicating that B1 actually inhibits BCL2. Thus it is questionable that B1 protein potentiates cell death via inhibiting BCL2, because binding to a compound does not necessarily mean that the activity of said compound is inhibited. For example, binding of a ligand to a receptor would actually enhance the activity of a receptor.

In view of the above, it would be undue experimentation to practice the claimed invention.

4. If Applicant could overcome the above 112, first paragraph, claims 5-8, 11, 23, 24, 44, 47, 48 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a DNA sequence of SEQ ID NO:2, does not reasonably provide enablement for a fragment or a portion of a DNA sequence of SEQ ID NO:2, which potentiates cell death The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

It is noted that a fragment or a portion could be as little as one or two nucleotides.

Claims 5-8, 11, 23, 24, 44, 47 and 48 are drawn to a DNA sequence or a portion of SEQ ID NO:2, encoding a fragment of SEQ ID NO:1, which fragment potentiates cell death.

The specification discloses that B1 protein or SEQ ID NO:1 enhances cell death not on its own presence, but requires the presence of cell death mediators, such as p55 TNF-R, Fas-R, MORT1, TRADD, RIP, ICE, ICH-1, but without direct interaction with these mediators (p.57, first and second paragraph, p.62, second paragraph). There is no disclosure of which fragment of B1 protein mediates cell death in the presence of cell death mediators. The specification further discloses that B1 contains a CARD domain (p.53). Although CARD domain usually serves as a region through which various proteins interact during the apoptotic signaling process intracellularly, said CARD domain from the claimed B1 protein does not seem to be necessary for potentiating cell death, because mutated B1 without the CARD domain still potentiates cell death (figure 5). Thus it is not clear which fragment of B1 protein is responsible for potentiating cell death. Further, the specification discloses, but without actual binding data, that preliminary results indicate that a truncated B1 having only the intermediate region and the C-terminal CARD region binds to BCL2 (p.36, Example 2(i)). The specification speculates that B1 may serve as an inhibitor of BCL2, which is known in the art to protect cells against apoptosis (p.57, third paragraph). However, there is no data indicating that B1 actually inhibits BCL2. Thus it is questionable that the intermediate region and the C-terminal CARD region is actually responsible for potentiating cell death via inhibiting BCL2, because binding to a compound does not necessarily mean that the activity of said compound is inhibited. For example, binding of a ligand to a receptor would actually enhance the activity of a receptor.

The instant specification thus fails to provide sufficient descriptive information, such as definitive strutural or functional features of the claimed polynucleotide encoding a fragment of SEQ ID NO:1, which potentiates cell death. In the absence of a teaching of how to obtain a fragment of SEQ ID NO:1, which potentiates cell death, it would be burden for one of skill in the art to make and use the claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Minh-Tam B. Davis whose telephone number is (703) 305-2008. The examiner can normally be reached on Monday-Friday from 9:30am to 3:30pm, except on Wesnesday

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tony Caputa, can be reached on (703) 308-3995. The fax phone number for this Group is (703) 308-4227.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0916.

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August 01, 2001

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